U.S. ACTIVITIES TO ADDRESS ANTIMICROBIAL RESISTANCE

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Antimicrobials have played an important role in livestock production as well as the treatment and prevention of infections in humans and animals. Subtherapeutic doses of certain antimicrobials have been used as growth promotants for over 40 years. The subject of antimicrobial resistance and its development is not new nor surprising; however, over the last few years, it has gained attention because of the potential public health impact. Antimicrobial resistance remains unclear. The development of antimicrobial resistance, its persistence and transmission, and even the public health impact are multifactorial. The role of risk factors such as duration, type, and dosage of antimicrobial use is also unclear. Data are limited on the prevalence of antimicrobial-resistant zoonotic bacteria in foods of animal origin and on the use of antimicrobials in agriculture and human medicine. There are problems with study designs involving the testing of representative sampling, the determination of sources, and tracing of animals.

CURRENT EFFORTS

Current programmes in the U.S. can be divided into surveillance, education, and research.

Surveillance

The Center for Veterinary Medicine (CVM) at the Food and Drug Administration (FDA), Animal Plant and Health Inspection (APHIS) and the Food Safety Inspection Service (FSIS) at the United States Department of Agriculture (USDA), and the Centers for Disease Prevention and Control (CDC), joined forces in 1996 to establish the National Antimicrobial Susceptibility Monitoring System, now referred to as the National Antimicrobial Resistance Monitoring System- Enteric Bacteria or NARMS-EB. This surveillance system proposed to monitor changes in susceptibilities of zoonotic pathogens from human and animal clinical specimens, from healthy farm animals, and from carcasses of food-producing animals at slaughter. The first organism selected was non-typhoid *Salmonella*. This system has two parallel arms: veterinary and human. Veterinary testing is conducted at USDA's Agricultural Research Service's Russell Research Center in Athens, GA while human samples are sent by 16 State Health Departments for testing at the National Center for Infectious Diseases, CDC. The 17 antimicrobials that are monitored were selected as representative antimicrobials or classes of antimicrobials used in animal and human medicine. In 1997, *Campylobacter* was added to the human surveillance; in 1998, *Campylobacter* and *E.coli O157:H7* were added to the veterinary surveillance.

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The goals and objectives of this surveillance system are to: 1) provide descriptive data on temporal trends of antimicrobial susceptibility in *Salmonella* from animal and human populations; 2)facilitate the identification of resistance in humans and animals as it occurs; 3) provide timely information to veterinarians, physicians, health officials; 4) prolong the life span of approved drugs by promoting prudent and judicious use of antimicrobials; 5) identify areas for more detailed investigations.

In 1998, CDC reported that there were 1476 *Salmonella* isolates, 315 *E.coli O157:H7* isolates, and 382 *Campylobacter*. Of the *Salmonella* isolates, 27% were resistant to one or more antimicrobials. Of the *Salmonella typhimurium* isolates, 53% were resistant to one or more; 32% had multi-drug resistant patterns characteristic of *DT 104*. Of *E.coli* isolates, 7.3% were resistant to one or more antimicrobials. Of *Campylobacter* isolates, 55% were resistant to one or more antimicrobials; 13.3 % were resistant to ciprofloxacin.

In 1998, CVM reported that 3318 *Salmonella* and 209 *Campylobacter* were tested. The amount of resistance varied depending on species and antimicrobial. For example, 38% of the *Salmonella* isolates were resistant to tetracycline and 35% were resistant to streptomycin. *Campylobacter* isolates from raw chilled broiler carcasses were tested against 8 antimicrobials. All isolates were susceptible to gentamicin and chloramphenicol. However, 60% of the isolates were resistant to tetracycline and 11% were resistant to ciprofloxacin.

Education

There are efforts by public health officials and veterinary and human medicine to educate consumers, physicians, veterinarians, and producers on the judicious use of antimicrobials. CDC currently has a programme aimed at patients, pediatricians, and infectious disease physicians on the prudent use of antimicrobials. This includes public health training seminars, brochures, and even an innovative approach of having prescription pads for physicians to prescribe care and help tips rather than antimicrobials. The American Veterinary Medical Association (AVMA) has established a Steering Committee on the Judicious Therapeutic Antimicrobial Use. This committee is comprised of federal consultants and experts that can review various issues, provide strategic planning, and direct future efforts to address antimicrobial resistance. The purpose of the Committee is to advise the Executive Board on ways to develop the guidelines for judicious therapeutic use of antimicrobials by veterinarians and continuing education programmes to raise the awareness of the profession. The Center for Veterinary Medicine has contracted with AVMA to have continuing educational materials created. The committee has encouraged and is currently advising on drafted guidelines for antimicrobial use for each species. For example, the National Pork Producer's Council is in the final stages of getting their guidelines approved.

Research

Research is ongoing and may consist of basic or applied research. General categories of research that were funded by USDA's Cooperative State Research Education and Extension

Service (CSREES) are: surveillance of antimicrobial resistance on farms; mechanisms of resistance development and resistance transfer; risk factors of resistance; alternatives to antimicrobials; and antimicrobial usage. Specific examples include: a project to demonstrate whether or not phenotypic and genotypic associations among antimicrobial resistant pathogens in humans and livestock exist; a project to measure antibiotic usage and development resistance of *Salmonella* in cattle; a project to look at vaccination in swine as an alternative; and projects to determine the levels of antimicrobial resistance in *Salmonella* in feed. An exciting new grant programme was initiated in 1999 by CSREES's National Research Initiative (NRI) division entitled, Epidemiologic approaches for food safety. This programme enables the awarding of larger-sized grants for population/field studies. Of the 9 grants awarded in 1999, at least 4 involved some research in antimicrobial resistance. There is other research being funded by federal agencies such as CVM, USDA's FSIS and Agricultural Research Service (ARS). ARS has a large programme in developing alternatives to antimicrobials such as competitive exclusion products and examining the development of antimicrobial resistance in *Salmonella DT104.*

U.S. Public Health Action Plan

The U.S. Public Health Action plan to combat antimicrobial resistance, when completed, is supposed to provide a blueprint for specific, coordinated federal actions to address the threat of antimicrobial resistance. It has been developed by an interagency task force on antimicrobial resistance that was organized in 1999. The task force is co-chaired by CDC, FDA, and the National Institutes of Health (NIH). But it also includes other federal agencies such as USDA, the Agency for Health Care and Policy Research, Department of Defense, the Veteran's Administration, the Environmental Protection Agency, and the Health Care Financing Agency. This plan, when finished, will reflect a broad-based consensus of federal agencies on actions needed to address antimicrobial resistance and solicited input from consultants from state and local agencies, universities, professional societies, pharmaceutical companies, health care delivery organizations, agricultural producers, consumer groups, and the public. A 3 day public meeting was held in July 1998 to solicit input from these consultants. The plan is divided into 4 sections: surveillance, prevention and control, research, and product development. The following are a sample of the major points within each section.

Surveillance: The greatest need is for a national antimicrobial resistance surveillance strategy. Currently there are existing surveillance networks that monitor some specific infectious diseases (e.g. tuberculosis, foodborne organisms, and NARMS), but there is a need to unify and coordinate the data and the resources. Increased emphasis and funding is being used to enhance epidemiologic and laboratory capacity and communication. There is a need to define roles and activities among personnel, facilities, and agencies. With the move to a unified system, it is essential that methods and data elements be standardized. This surveillance system has to be sensitive and flexible and must provide information to be disseminated back to public health officials, physicians, veterinarians, and federal, state, and local officials. Available and accurate drug susceptibility data are essential for the national resistance system. This data will be dependent on the standardization of methods and data elements. A part of

this system will include the improved surveillance for antimicrobial resistance in agricultural settings (animals and plants).

Secondly, monitoring is an essential part of surveillance. Monitoring of antimicrobial drug use both in humans and non-human settings is essential. Innovative methods for collecting such data will be required. For example, is it possible to conduct periodic surveys of food animal producers and veterinarians? Confidentiality of information that is gathered is critical. Currently, on-farm information is collected by USDA's APHIS through their National Animal Health Monitoring System on selected species. This effort is dependent on federal funding and the collaboration of producers. Monitoring of antimicrobial drug use in fruit and vegetable production, in food processing, and even in the pet population is also needed.

Prevention and control: Prudent drug-use policies for antimicrobials are needed in agricultural (animal and plant) and human settings. It is essential that there is a method by which the effectiveness of these policies can be evaluated. Better diagnostic tests, particularly at point-of-care, are required to allow for less prescribing of antimicrobials. Another method of decreasing the use of antimicrobials is better infection control and reduction of infection transmission. Although hospitals have had existing programmes in hospital infections, more efforts are needed.

Prevention and control of antimicrobial resistance must include a comprehensive, multi-faceted programme. This will involve educational and behavioral interventions; the improvement of our understanding of potential risks and benefits of antimicrobial use; and the study of animal and human waste and possible soil and environmental contamination. Prevention and control in agricultural settings will involve a look at animal husbandry and food production practices and the development of the new framework document for new antimicrobials by CVM. Additional research on the risk of development and transfer of resistance related to the use of antimicrobial drugs in food and non-food is needed to help develop and implement prevention and control programmes.

Research: It is essential to identify and fill the gaps and needs in the field of antimicrobial resistance research. Some prime examples for study are the epidemiology of resistance genes; mechanisms of antimicrobial resistance emergence, acquisition, spread and persistence; effects of antibiotics used as agricultural growth promotants on microbes; and the variations in drug use regimens. For research to continue, it is important to augment the research infrastructure. This involves increased funding, an awareness about the sources of funding, and an increased number of experts. Finally, it is essential that there is translation of research findings into innovative clinical products.

Product development: It is important to identify and fill current and projected gaps in our arsenals of drugs. There needs to be development of urgently needed drugs, vaccines, and diagnostics. Most importantly, this involves some type of incentives for this development. For example, the approval process needs to be simpler. Likewise, there is a need for the production of veterinary drugs. The financial incentive for new veterinary antimicrobials is

not high. Alternatives to antimicrobials such as vaccines, immune stimulators, and competitive exclusion products are important areas for development.

FUTURE DIRECTIONS

Surveillance

There is an existing infrastructure for surveillance, and the NARMS-EB system has made great strides in the surveillance of antimicrobial resistance. Currently there is momentum for the enhancement of epidemiologic and laboratory capacity. This funding could be available for veterinary diagnostic laboratories. Veterinary diagnostic laboratories could be sentinel sites for antimicrobial resistance and even food borne pathogens (similar to FoodNet). In fact, veterinary diagnostic laboratories as sentinels have been mentioned in national strategic planning efforts for food safety. How do we make NARMS-EB better? How can we better utilize the National Animal Health Monitoring System? Standardization of methodologies and data elements between veterinary laboratories and surveillance systems are needed. Once this effort is coordinated, the ability to merge with human surveillance networks may be possible.

Research

Research is needed in many areas. Although evidence demonstrates that antimicrobial resistance can be transferred from animals to humans, little is known about the true public health impact. Data are needed on the prevalence of antimicrobial resistance on the farm and how this prevalence relates to antimicrobial resistance in humans. Research on the mechanisms of development, persistence, and transference of antimicrobial resistance is urgent. Information on drug usage, dose, and duration could provide insight into possible prevention and control programmes. For example, is it high doses of antimicrobials given short term or low doses of antimicrobials given long term that cause the most antimicrobial resistance? Finally, research determining risk factors is essential. Risk factor data are required for risk assessments and, most importantly, to develop intervention strategies. As intervention strategies and management practices are implemented, the impact of these on antimicrobial resistance must be evaluated. What are the outcome measures?

Education

There is an urgent need for educational efforts on judicious use of antimicrobials by health care professionals and producers. Aggressive educational programmes targeted at veterinary students are appropriate. Veterinary students must learn to educate clients on the risks and benefits of antimicrobials, even in small animal medicine. Why not follow the direction of human medicine and use the media as a way to educate consumers? For example, instead of advertising the newest arthritis medicine for dogs and cats, why not advertise the prudence in not asking for antimicrobials for both the health of the pet and the owner?

Prevention/Control

A major effort is underway by CVM in the development of the framework document for new antimicrobials. The framework document sets out a conceptual risk-based process for evaluating the microbial safety of antimicrobial drugs intended for food-producing animals. Categorization of newly proposed antimicrobials will be based on their importance to human medicine. For example, category 1 will result in little or no resistance transfer to humans. Category 2 would require a predefined level of maximum resistance transfer to be established. Pre-approval data will be required to show that the level of resistance transfer from animals to humans will be safe. Depending on some of the categories, there may be post-approval studies required. Finally, new and innovative management practices or quality assurance programmes must be implemented at the farm level. The impact of these strategies must be evaluated.